Stimulus Frequency Dependency of Postive BOLD (PBOLD) and Post Stimulus Undershoot (PSU)

U. E. Emir[1], Z. Bayraktaroglu[2], A. S. Alper[1], A. Ademoglu[1], C. Ozturk[1], and T. Demiralp[2]

[1]Institute of Biomedical Engineering, Bogazici University, Istanbul, Turkey, [2]Istanbul Faculty of Medicine, Department of Physiology, Istanbul University, Istanbul, Turkey

Introduction

The dependency of PBOLD and CBF based fMRI on the temporal frequency of the stimulation has been studied before [1-6] where an increase in PBOLD has been reported up to 8 Hz, which was followed by either a decrease or a plateau for higher frequencies. In contrast to the only observed fMRI peak around 8 Hz, also observed in PET studies [7-8], EEG responses in similar experiments have shown additional peaks specifically for stimulus frequencies beyond 8 Hz such as 10, 20, 40 Hz [9]. However, effects of these stimulus frequencies have not yet been sufficiently studied with fMRI. So far, most of the researches on BOLD transients were studied with input stimulus frequencies up to 30Hz. Another interesting question is how BOLD transient components including the PSU change their behavior when stimulated with a finer frequency resolution up to 40 Hz. In this study we focused on PBOLD and PSU responses during to the stimulation frequencies beyond 8Hz and explored the additional local maxima emerging from a stimulation scheme with a finer frequency resolution. The correlation between the PBOLD and PSU across different stimulation frequencies was analyzed to explore the underlying physiological mechanisms of these two transients.

Methods and Data Analysis

All experiments with were conducted on Siemens 1.5T Tesla MR System at Istanbul University Istanbul Medical School. Five healthy human volunteers participated in this study. Informed consent was obtained from all subjects after the study was explained. Photic stimulation was applied using LEDs coupled to fiber bundle. Fiber bundles placed on both glasses of a welding goggle transferred the light into the magnet room. In front of the bundles, a piece of special optically diffusible material was used to diffuse the light and protect subjects eyes. The stimuli were presented at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 18, 20, 22, 24, 28, 32, 36, 40 and 44 Hz.

A single shot T^*_2 weighted gradient echo planar imaging sequence was used for BOLD measurements. Ten transverse slices of 64x64 were acquired with a slice thickness of 3.5 mm positioned through the visual cortex (TR 2000ms, flip angle 90 degrees). The fMRI protocol consisted of two blocks, 15 images "OFF" and 15 images "ON" periods interleaved with 30 images "OFF" period. At the end of the study, 90 images were acquired. A standard 3D MPRAGE sequence was used for high resolution anatomic scan. fMRI data were processed by FSL software package. Images were registered in order to remove motion artifacts. Time-series statistical analysis was carried out using FILM with local autocorrelation correction [9]. A fixed-effect group analysis was performed to combine statistical parametric maps of the first level analysis for individual subjects across all stimulation frequencies. This resulted in a Z-score map of statistically significant stimulus related activity across all stimulus frequencies for each subject. Z (Gaussianised T/F) statistic map was thresholded using clusters determined by $Z>3$ and a (corrected) cluster significance threshold of $P=0.05$. Then, a mask that consists of a most active cluster including 200-250 voxels in the visual cortex was created for each subject. For each stimulation frequency of each subject, average BOLD signal time course was computed from all activated voxels within the mask. The percent change of the BOLD signal is defined as the absolute difference between the BOLD and the baseline. The baseline signal level was defined as the average signal during the time period of 10s before the stimulus was turned on. PBOLD was quantified as the average value of the BOLD response between 20-30 s after the stimulus onset, and PSU was quantified as the average BOLD value between 10-30 s after the stimulus offset. In order to eliminate intersubject variability, an additional normalization was performed by dividing the percent change responses due to different frequencies by the maximum BOLD percent change response observed for each subject

Results

The functional map due to blocked visual stimulation from one of the subjects, superimposed onto the anatomical image, is shown in Fig. 1. Figure 2 is the plot of mean normalized percent change for all nine subjects as a function of stimulus frequency. The global maximum of BOLD response was at 8 Hz, which was significantly higher compared with the mean BOLD amplitude along the whole stimulation frequency range between 2 and 44 Hz ($p<0.03$). Other local maxima were observed for stimulation frequencies at 16, 24 and 40 Hz. The 8 Hz peak was significantly higher than BOLD responses between 2 and 13 Hz ($p<0.02$). The peak at 16Hz was significantly higher than BOLD responses between 13 and 22 Hz ($p<0.05$) and the local maximum at 24Hz was significantly higher than responses between the 22 to 28 Hz ($p<0.05$). The comparison of the local maximum at 40 Hz with the mean amplitude within the 28 to 44 Hz range turned out to be non-significant. The correlation coefficient between the PBOLD and PSU profiles through all the stimulation frequencies was computed as $r=0.391$; $p=0.059$. The correlation analyses indicate that PBOLD amplitudes were not correlated with PSU along the whole frequency range. However, a careful observation of the profiles within the frequency range between 1 and 13 Hz reveals that the PSU amplitudes changed in-line with the PBOLD. On the other hand, such a positive correlation did not exist for the frequency range between 13 and 44 Hz with extra negative deflections between 13 and 22 Hz implying for a possible negative correlation. The absolute amplitude values of PBOLD and PSU showed a significant positive correlation between 1 and 13 Hz range ($r2= 0.615$, $p<0.03$), whereas they were not correlated at all between 13 and 44 Hz ($r=0.167$; $p=0.603$).

Discussion and Conclusion

The literature on the fMRI changes due to temporal frequency of visual stimuli mainly focuses on positive BOLD peak around 8 Hz and reports either a decrease or a plateau for higher stimulus frequencies. However, our results based on visual stimuli applied with a finer resolution for higher stimulation frequencies show that it does not monotonically decay but shows some significant secondary peaks around 16 and 24 Hz. To the best of our knowledge, this is the first observation of the local peaks beyond 8 Hz in BOLD fMRI studies. With this study we also explore in detail the underlying neurovascular coupling dynamics of BOLD transients, specifically amplitude of PBOLD and PSU. By comparative analysis of PBOLD and PSU changes across stimulation frequencies, we report two different patterns for stimulation frequencies below and above 13 Hz which, when discussed in the light of electrophysiology literature, could reveal important hints on the underlying neurovascular mechanisms with regard to their relation to inhibitory and excitatory neuronal activity.

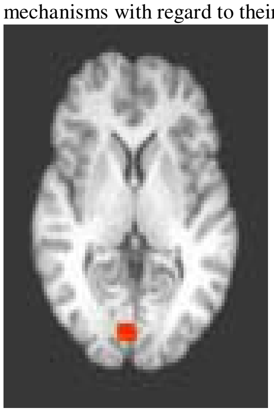

Figure 1 Functional map obtained from fMRI due to visual stimulation from one subject, overlaid onto the anatomic image

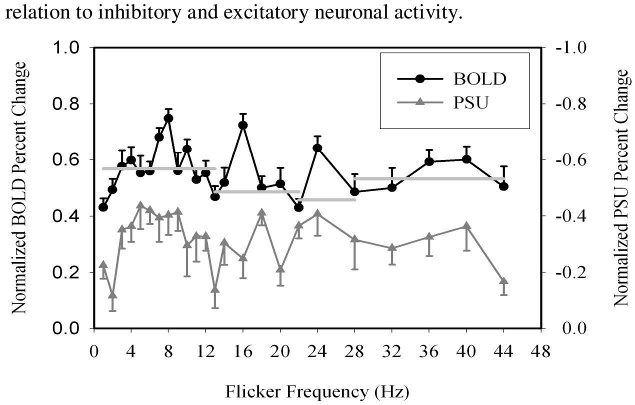

Figure 2 Normalized PSU (Right y axis) and PBOLD (Left y axis) change. Note that the scale of the right y axis is inverted for better visualization. The error bars represent the standard errors. Significance of the local maxima was tested against the mean of the adjacent frequencies (indicated as straight gray lines).

[1] Srinivasan R. F. et al., Exp Brain Res, 180, 677, 2007.
[2] Mirzajani A. R. et al., Physiol Meas, 28, 547,2007.
[3] Parkes L. M. F et al., Neuroimage, 21, 236, 2004.
[4] Singh M K et al., Magn Reson Med, 49, 108, 2003.
[5] Ozus B. L. et al., Magn Reson Imaging, 19, 21, 2001.
[6] Thomas C.G. et al., Magn Reson Med. 40, 203, 1998.
[7] Fox P.T. et al., J Neurophysiology. 51, 1109, 1984.
[8] Fox P.T. et al., Ann Neurol. 17, 303, 1985.
[9] Herrman C. S., Exp Brain Res, 137, 346, 2001.
[10] Woolrich M. W. R. et al., Neuroimage, 14, 1370, 2001.